

ternalized at the nape of the neck, and the incision site was sutured closed with surgical staples. The cannula was flushed with heparinized saline (20 units/mL) and attached to a Gould Statham pressure transducer (Model P23ID), and blood pressures and heart rates were recorded on a Beckman R-611 polygraph recorder. Rats were placed unrestrained except for the catheter tether into individual cages and allowed 2 h to recover from surgery. Drugs were administered ip as solutions in 20% DMF or po as suspensions in 5% PEG 400/1% methocel. Blood pressures and heart rates were monitored for 5-6 h and recorded at 0.5-h intervals.

Registry No. 1, 105763-92-6; 2, 105763-93-7; 3, 105763-94-8; 4, 95333-69-0; 5, 105763-95-9; 6, 105763-96-0; 7, 95333-70-3; 8, 105763-97-1; 9, 105763-98-2; 10, 105763-99-3; 11, 95333-91-8; 12, 95333-90-7; 13, 105764-00-9; 14, 105764-01-0; 15, 95333-88-3; 16, 105764-02-1; 17, 95333-53-2; 18, 105764-03-2; 19, 95333-51-0; 20, 101913-05-7; 21, 95460-09-6; 22, 95333-54-3; 23, 95333-50-9; 24,

95333-61-2; 25, 95333-79-2; 26, 95333-71-4; 27, 95333-72-5; 28, 95333-59-8; 29, 95333-62-3; 30, 105764-04-3; 31, 95333-73-6; 32, 95333-52-1; 33, 95333-74-7; 34, 105764-05-4; 35, 104197-16-2; 36, 23269-10-5; 37, 95333-58-7; 38, 95333-75-8; 39, 95333-76-9; 40, 95333-48-5; 41, 95333-77-0; 42, 95333-80-5; 43, 95333-83-8; 44, 95333-64-5; 45, 95333-78-1; 46, 95333-66-7; 47, 95333-82-7; 48, 95333-68-9; 49, 95333-49-6; 50, 95333-81-6; 51, 95333-57-6; 52, 95333-60-1; 53, 20532-06-3; 54, 105764-06-5; 55, 105764-07-6; 56, 82772-93-8; 57, 101471-20-9; 58, 461-96-1; 59, 64248-63-1; 60, 32085-88-4; 61, 84315-23-1; 62, 84315-24-2; 63, 95333-92-9; 64, 95333-93-0; 65, 95333-94-1; 66, 90418-21-6; 67, 95333-95-2; 68, 95333-96-3; 69, 95333-97-4; 70, 101913-07-9; DBH, 9013-38-1; *p*-OHCC₆H₄CO₂Me, 1571-08-0; NH₂CH₂CH(OMe)₂, 22483-09-6; HO₃SCl, 7790-94-5; *p*-MeOC₆H₄CO₂H, 100-09-4; (HO₂C)₂CH₂, 141-82-2; Ph(CH₂)₂NH₂, 64-04-0; 2,6-dimethylbenzaldehyde, 1123-56-4; 3,5-dichloroanisole, 33719-74-3; 2,4-difluoroaniline, 367-25-9; 3,5-dichlorobenzaldehyde, 10203-08-4; dopamine, 51-61-6; norepinephrine, 51-41-2.

Dopamine Autoreceptor Agonists: Resolution and Pharmacological Activity of 2,6-Diaminotetrahydrobenzothiazole and an Aminothiazole Analogue of Apomorphine

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The enantiomers of the aminothiazole analogues of the known dopaminergic agonists apomorphine (1) and 2-aminohydroxytetralin (2) have been prepared. The absolute configurations of the enantiomers of 2,6-diaminotetrahydrobenzothiazole have been established by X-ray crystallographic analysis. Dopamine (DA) autoreceptor agonist activities of the compounds were evaluated. Testing revealed (–)-5, the *S* enantiomer, to be the most active compound tested (inhibition of GBL accelerated dopamine synthesis and inhibition of α -methyltyrosine-induced decline of DA). In addition (–)-5 does not exhibit stereotyped behavior, suggesting a pronounced selectivity for DA autoreceptors.

Dopamine (DA) receptor agonists that stimulate the DA autoreceptor in the brain represent a novel therapeutic approach in the treatment of schizophrenia by reducing the release of DA presynaptically.¹⁻³ Those selective DA agonists should be devoid of the untoward dyskinetic side effects of the classical neuroleptics. Apomorphine exerts presynaptic DA receptor activity.

Doses of (*R*)-(–)-apomorphine (1), at least 1 order of magnitude below that required for producing stereotyped behavior in rats, inhibit DA synthesis and also cause a reduction in DA release.⁴⁻⁶ The *S*-(+)-enantiomer of apomorphine has an approximately 10-fold lower affinity to presynaptic DA receptors.⁷

Investigation of hydroxy derivatives of 2-aminotetralins 2 that may be regarded as subunits of apomorphine revealed that dopaminergic activity appears to be dependent upon the configuration of carbon C-2 and upon the position

of the phenolic hydroxy group.^{8,9}

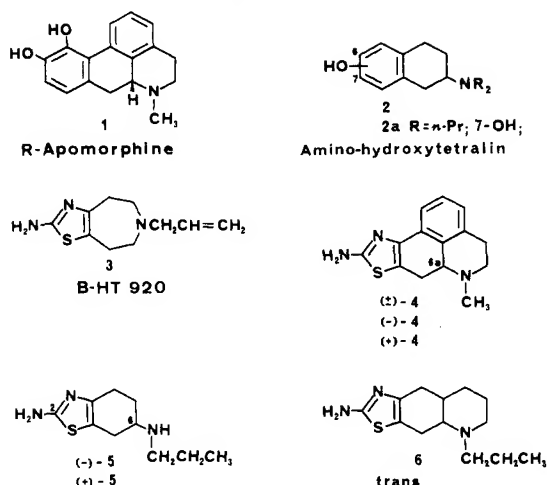
Recently, it has been shown by Andén that the aminothiazoloazepine derivative B-HT 920 (3) inhibits the synthesis and the α -methyltyrosine-induced decline of DA in the brain of rodents. From these findings Andén concluded that B-HT 920 is a relatively selective DA receptor agonist that acts presynaptically.^{10,11}

In order to study the influence of the exchange of the catechol subunit of DA agonists for the aminothiazole moiety on presynaptic DA receptor activity, we prepared the enantiomers of aminothiazolo analogues 4 and 5¹² of apomorphine and aminotetralin, respectively.

Chemistry. The aminothiazole analogue 4 of apomorphine was synthesized by using a previously published procedure.¹³ Optical resolution was accomplished with L- and D-tartaric acid, respectively. The enantiomeric tartrates thus obtained were converted into the corresponding dihydrochlorides.

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The 2,6-diaminotetrahydrobenzothiazoles (5) were prepared as outlined in Scheme I. 4-Acetamidocyclohexanone was brominated in AcOH and immediately treated with thiourea to give the acetamido thiazole derivative 7. The acetyl group was removed with 48% aqueous HBr to give 8. The latter was resolved into its enantiomeric forms as described for compound 4. The enantiomers were converted into the corresponding bases which, on reaction with propionic anhydride, afforded the enantiomeric propion-amido compounds (+)-9 and (-)-9. Reduction with di-borane gave the propylamino compounds (+)-5 and (-)-5. The conditions of these reactions are unlikely to affect the chiral centers of the compounds. In order to determine the enantiomeric purities, (+)-5 and (-)-5 were converted into the corresponding D-(+)-mandelic acid salts. ^{13}C NMR spectra of the diastereomeric mandelates with addition of the shift reagent tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium ($\text{Yb}(\text{fod})_3$) indicated enantiomeric purity of above 95% (detection limit) for both enantiomers.

An X-ray diffraction study of the L-(+)-tartaric acid salt of (-)-8 was undertaken in order to determine the absolute configuration of the amine with reference to the known configuration of L-(+)-tartaric acid. The chiral carbon in position 6 was shown to have *S* configuration (Figure 1).¹⁴ The absolute configuration of (+)-8 as well as of the enantiomers of 9 and 5 are thus also established.

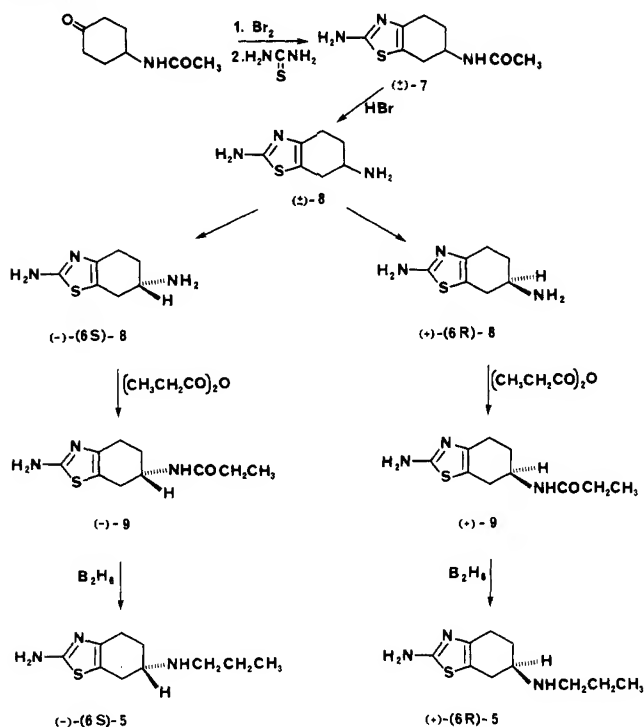
Compound 6 was prepared as recently published.^{13,15}

Pharmacology. Agonistic activity on the presynaptic DA receptor was determined as previously described^{10,11} by measuring the inhibition of γ -butyrolactone (GBL) induced acceleration of DA synthesis in rat corpus striatum (i.e., DOPA accumulation in DOPA decarboxylase inhibited rats) and by measuring the utilization of DA in the whole brain of rats following inhibition of tyrosine hydroxylase with α -methyltyrosine methyl ester (α -MT).

Results and Discussion

The autoreceptor activity of compound 4 shown by means of the utilization of DA and by inhibition of DA synthesis (Table I) resides almost exclusively in the (-)-enantiomer. Results with (*R*)-(-)-apomorphine are given

Scheme I



for comparison. Such a stereoselective effect in favor of the levoisomer (-)-4 is in accordance with the situation for apomorphine. The chiral carbon 6a of (-)-4, thus, is assumed to have the same absolute configuration as the corresponding carbon of (*R*)-(-)-apomorphine and to be *R*. This 6a*R* configuration with the nitrogen bent away from the plane of the thiazole ring would fit, moreover, into the central DA receptor according to the prerequisites of Freeman and McDermid.¹⁶

Superimposition of (-)-4 and (*R*)-(-)-apomorphine in respect to an optimal fit of the thiazole and the hydroxylated ring as well as the common ring nitrogen shows that the orientation of the amino group of the thiazole ring corresponds to that of a hydroxy group between the position 9 and 10 of apomorphine, but shifted more toward the 10-position (Figure 2). From the 8-, 9-, 10-, and 11-hydroxyapomorphines investigated so far,^{17,18} only the 11-hydroxy derivative shows dopaminergic activity, although weaker than apomorphine itself. Isoapomorphine, the 9,10-dihydroxy isomer, is devoid of central DA agonist activity.^{17,19} In the McDermid model, the missing activity of isoapomorphine is explained with the steric effect of the unsubstituted benzene ring.¹⁶

Octahydrothiazolo[4,5-*g*]quinoline 6, a compound lacking the fused benzene ring, and its enantiomers have recently been reported by Schaus et al.¹⁵ to possess dopaminergic activity (prolactin inhibition and turning behavior in the lesioned rat). Data obtained with our models and presented in Table I are consistent with the speculation that loss of the bulky benzene enhances autoreceptor ac-

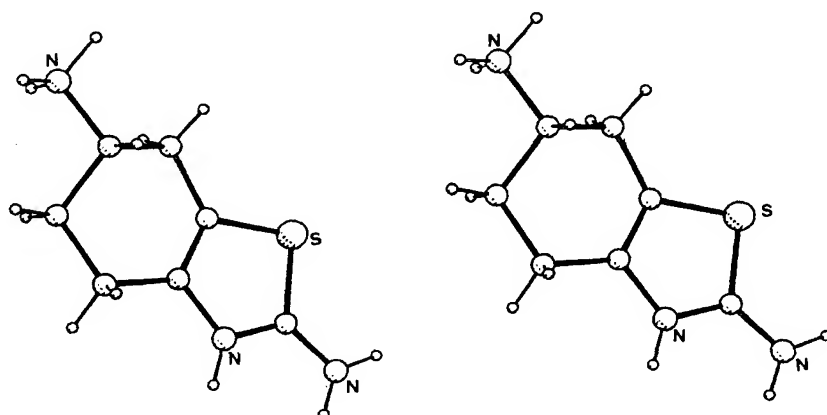
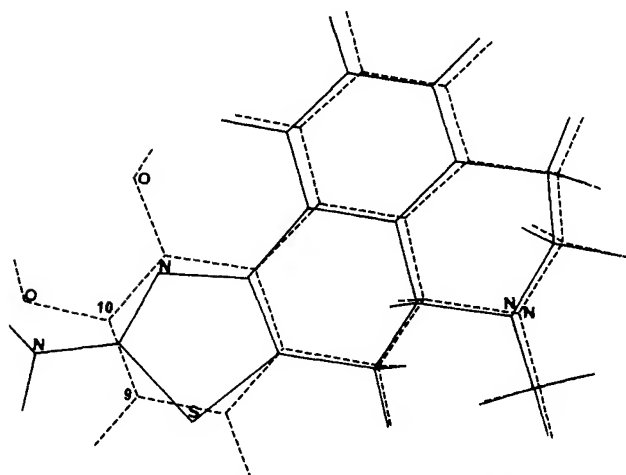
- (14) The X-ray structural analyses were kindly undertaken by J. P. Declercq, B. Tinant, and M. van Meersche at the Laboratoire de Chimie Physique et de Cristallographie, Université Catholique de Louvain, Louvain la Neuve, Belgium.
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Table I. Biological Data

compd	dose, mg/kg	L-DOPA accumulation ^{a,c}		DA utilization ^{b,c}		[³ H]spiperone ^e receptor binding: IC ₅₀ , nM
		nmol of L-DOPA/g of tissue weight ^d corpus striatum	% difference compared to saline	pmol of DA/g of tissue weight ^e total brain without cerebellum	% difference compared to saline	
saline		24.1 ± 0.7 (4) ^f		2774 ± 111 (7) ^f		
(±)-4	10.0	14.9 ± 1.1 (4)***	-38	3721 ± 72 (6)***	+34	7 000
(+)-4·2HCl·0.5H ₂ O	10.0	24.4 ± 2.7 (4)	+1	2441 ± 33 (6)*	-12	>100 000
(-)-4·2HCl·0.5H ₂ O	10.0	20.1 ± 1.2 (4)*	-16	3917 ± 72 (6)***	+41	2 900
6·2C ₄ H ₄ O ₄	10.0	9.1 ± 0.7 (5)***	-62	4863 ± 144 (4)***	+75	310
(+)-8·2HCl	10.0	NT ^g		2441 ± 131 (8)	-12	>100 000
(-)-8·2HCl	10.0	NT ^g		2317 ± 124 (8)*	-17	57 000
(+)-5·2HCl	1.0	19.0 ± 2.5 (4)	-21	5104 ± 52 (4)***	+84	43 000
(-)-5·2HCl	1.0	11.3 ± 1.7 (4)***	-53	6417 ± 111 (4)***	+131	4 700
apomorphine	1.0	8.9 ± 0.3 (3)***	-63	4008 ± 372 (8)***	+44	110

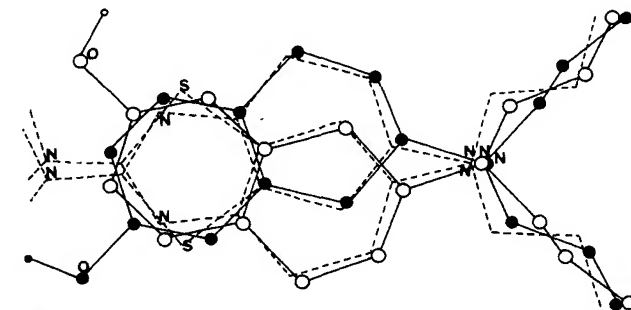
^a L-DOPA accumulation elicited by injections of GBL (750 mg/kg) and NSD 1015 (100 mg/kg). ^b DA content following α -MT (250 mg/kg). ^c For experimental details, see Experimental Section. ^d Saline and drug treatment after stimulation with NSD 1015 and GBL. ^e Saline and drug treatment after injection of α -MT. ^f Values represent the mean SEM with the number of experiments in parentheses. Statistical significances were calculated by using the Student's *t* test. Asterisks indicate significant differences from control values: (*) *p* < 0.05, (**) *p* < 0.01, (***) *p* < 0.001. ^g Not tested due to inactivity in the DA utilization test.

**Figure 1.** Molecular structure from X-ray determination of L-(+)-tartaric acid salt of resolved (-)-8 (stereoscopic pair).**Figure 2.** Superimposition of apomorphine (---) and (-)-4 (—).

tivity compared to apomorphine and compound (-)-4.

The most active compounds of this study are the enantiomers of 2-amino-6-(propylamino)tetrahydrobenzothiazole (5) whereas the parent compound 8 with primary 6-amino function is completely inactive. Comparison of the enantiomers of 5 shows that the (*S*)-(-)-5 exceeds DA increase by 50% over that of its *R*-(+)-counterpart (DA utilization test).

In a recent study the 7-hydroxy-2-(*N,N*-dipropylamino)tetralin (7-OH-ATN) (2a) proved to be the most

**Figure 3.** Superimposition of the enantiomers of 5 (---) and 2a (—). Hydrogen atoms are omitted for clarity.

selective presynaptic agonist of the monohydroxy and dihydroxy derivatives tested.²⁰ Structural superimposition of 7-OH-ATN and compound 5 with respect to the same projection of the alkylated nitrogen and the center of the aromatic ring reveals that the direction of the 2-amino group linked to the thiazole ring of either the *R* or *S* enantiomer of 5 is between those of the 7-hydroxy groups of the *R* and *S* enantiomer of 7-OH-ATN (Figure 3). Neither of the enantiomers of compound 5 exhibits stereotyped behavior in mice (postsynaptic agonist activity) up to 40 mg/kg.

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The binding studies with use of [³H]spiperone as ligand showed a 40-fold lower affinity of (–)-5 compared with apomorphine. The results suggest that in 5 the 2-aminothiazole group shows the appropriate orientation to evoke presynaptic activity. Apart from this, the observation that linear *trans*-octahydro-7,8-dihydroxybenzo[*g*]quinoline,²¹ i.e. an isoapomorphine congener lacking the unsubstituted benzo-fused ring, lacks DA-like activity shows that not only the benzo-fused ring but also the vectorial direction of the lone pair of electrons on the nitrogen may be improper for receptor interaction in compounds with an octahydroquinoline moiety.^{21,22} There is a freely rotatable *N*-propylamino substituent in compound 5. This free rotation allows an unhindered direction of the positive charge under physiological conditions that cannot be adopted by the compounds 4 and 6. This may explain the comparatively weaker potency of 4 and 6 relative to that of 5.

Experimental Section

Chemistry. Melting or decomposition points were determined in a Büchi 510 apparatus in open capillary tubes and are uncorrected. Microanalyses agree, unless otherwise stated, with calculated values within $\pm 0.4\%$. IR and NMR spectra are consistent with assigned structures.

(\pm)-9-Amino-6-methyl-5,6,6a,7-tetrahydro-4H-benzo[*de*]thiazolo[4,5-*g*]quinoline (4). Compound 4 was prepared according to the procedure of Berney and Schuh¹³ in 58% yield: free base m 201–203 °C (lit.¹¹ dihydrochloride mp 200 °C dec).

Resolution of (\pm)-9-Amino-6-methyl-5,6,6a,7-tetrahydro-4H-benzo[*de*]thiazolo[4,5-*g*]quinoline (4). To a suspension of racemic 4 (6.6 g, 0.026 mol) in 60 mL of water was added L-(+)-tartaric acid (3.9 g, 0.026 mol) [Aldrich: $[\alpha]_D^{20} +12^\circ$ (c 20, CH₃OH)]. The mixture was heated to reflux for 10 min and then filtered. After the mixture was allowed to stand for 1 day, 7.8 g of gray crystals were collected. This L-(+)-tartrate salt was crystallized five times from 50 mL of water to yield 0.9 g of the pure compound, mp 223–224 °C. Further crystallizations did not change the specific rotation of the free base liberated from samples of the tartrate after each recrystallization: $[\alpha]_D^{25} +168.8^\circ$ (c 0.35, acetone); ee > 96% (detection limit), determined by ¹³C NMR spectroscopy with Yb(fod)₃ as the chiral shift reagent. The pure L-tartrate was treated in aqueous ammonia, and the liberated base was extracted with EtOAc. After washing (H₂O) and drying (MgSO₄), the extract was converted into the dihydrochloride salt to give 0.5 g of (+)-4·2HCl·0.5H₂O, white powder, mp 274–276 °C; $[\alpha]_D^{25} +88^\circ$ (c 0.1, H₂O).

The combined mother liquors of the above L-tartrate were treated with aqueous ammonia, and the liberated free base was extracted with EtOAc, washed, dried, and evaporated to dryness. The remaining 4 g of solid was suspended together with D-(–)-tartaric acid (2.4 g, 0.016 mol) [Aldrich: $[\alpha]_D^{20} -12^\circ$ (c 20, H₂O)] in 60 mL of water. The separating crystals were treated as described above to give 1.4 g of the pure compound, mp 218–220 °C; specific rotation of the base: $[\alpha]_D^{25} -170.2^\circ$ (c 0.35, acetone). The pure D-tartrate was converted into the corresponding base and the dihydrochloride as described above for the L-tartrate. (–)-4·2HCl·0.5H₂O was obtained, 0.9 g, mp 276–277 °C; $[\alpha]_D^{25} -89.5^\circ$ (c 0.2, H₂O).

***trans*-2-Amino-4,4a,5,6,7,8,8a,9-octahydro-5-propylthiazolo[4,5-*g*]quinoline Difumarate (6).** Compound 6 was prepared via a multistep synthesis previously described,^{15,23} mp 238–239 °C.

6-Acetamido-2-amino-4,5,6,7-tetrahydrobenzothiazole (7). To a solution of 4-acetamidocyclohexanone²¹ (31 g, 0.2 mol) in

300 mL of AcOH was added Br² (32 g, 0.2 mol) at 60 °C with stirring. After continuous stirring for 1 h, thiourea (30.4 g, 0.4 mol) was added. The mixture was refluxed for 1 h, evaporated, diluted with 200 mL of water, and made alkaline. The precipitate was filtered off and washed with water and CH₃OH, giving 26 g (46%) of 7, mp 172–173 °C; ¹H NMR (Me₂SO-*d*₆) δ 7.08 (d, *J* = 8 Hz, 1 H), 5.62 (s, 2 H), 4.22 (m, 1 H), 2.84 and 2.41 (m, 2 H), 2.56 (m, 2 H), 1.68–2.08 (m, 2 H), 1.90 (s, 3 H). Anal. (C₁₀H₁₅N₃OS) C, H, N.

(\pm)-2,6-Diamino-4,5,6,7-tetrahydrobenzothiazole Dihydrochloride ((\pm)-8·2HCl). A mixture of 7 (7.2 g, 0.025 mol) and 47% aqueous HBr (72 mL) was refluxed for 15 h. After cooling, the precipitate was filtered off and washed with cold water and acetone, giving 7.8 g of (\pm)-8·2HBr, which was converted into its dihydrochloride salt. This was recrystallized from methanol to give 5.5 g (91%) of (\pm)-8·2HCl, mp >300 °C; ¹H NMR (CD₃OD/D₂O, 1:1) δ 3.54–3.94 (m, 1 H), 1.76–3.24 (m, 6 H), NH₂ in the solvent blind peak. Anal. (C₇H₁₁N₃S·2HCl) C, H, N.

Resolution of (\pm)-2,6-Diamino-4,5,6,7-tetrahydrobenzothiazole (8). To a suspension of the base of racemic 8 (16.9 g, 0.1 mol) in 250 mL of water was added L-(+)-tartaric acid (3 g, 0.1 mol) at 75 °C. While the mixture was allowed to stand for 1 day at room temperature, a precipitate formed, which was collected and recrystallized three times from water, giving 15 g of white crystals, mp 135 °C. Further recrystallizations did not change the specific rotation of the base: $[\alpha]_D^{20} -94.2^\circ$ (c 1, CH₃OH). The pure crystalline L-(+)-tartrate dihydrate was suspended in 20 mL of water and concentrated aqueous HCl was added dropwise until a clear solution resulted. After the addition of 85% aqueous KOH (35 mL) at 10 °C, the free base precipitated in white crystals, which were collected, washed with ice-water, and dried, giving 7 g of (–)-8, mp 229–231 °C; ee > 96% (detection limit), determined with Yb(fod)₃ as chiral shift reagent. Dihydrochloride salt (from methanol): mp >315 °C. Anal. (C₇H₁₁N₃S·2HCl) C, H, N.

(–)-2-Amino-6-propionamidotetrahydrobenzothiazole ((–)-9). To a mixture of (–)-8 (3.4 g, 0.02 mol) and triethylamine (2.2 g, 0.02 mol) in 50 mL of anhydrous THF was added propionic anhydride (2.9 g, 0.022 mol) dropwise at –5 °C. After the mixture was stirred for 2 h at –5 °C, concentrated aqueous ammonia (2 mL) was added and stirring was continued for 15 min. The mixture was concentrated in vacuo. The residue was dissolved in water and saturated with K₂CO₃. The resulting solution was extracted with EtOAc, the organic layers were collected and dried (MgSO₄), and the EtOAc was removed in vacuo. The resulting crystals were collected and washed with acetone to afford 4.1 g (90%) of (–)-9, mp 187–188 °C; $[\alpha]_D^{20} -69.0^\circ$ (c 1, CH₃OH); ¹H NMR (CD₃OD) δ 4.14 (m, 1 H), 1.52–3.07 (m, 6 H), 2.21 (qu, *J* = 8 Hz, 2 H), 1.12 (t, *J* = 8 Hz, 3 H), NH₂ in the solvent blind peak. Anal. (C₁₀H₁₅N₃OS) C, H, N.

(+)-2-Amino-6-propionamidotetrahydrobenzothiazole ((+)-9) was obtained from (+)-8 in the same manner as (–)-9 in 84% yield, mp 186–187 °C; $[\alpha]_D^{20} +67.5^\circ$ (c 1, CH₃OH); ¹H NMR (CD₃OD) δ 4.15 (m, 1 H), 1.56–3.09 (m, 6 H), 2.30 (qu, *J* = 8 Hz, 2 H), 1.13 (t, *J* = 8 Hz, 3 H), NH₂ and NH in the solvent blind peak. Anal. (C₁₀H₁₅N₃OS) C, H, N.

(–)-2-Amino-6-propyltetrahydrobenzothiazole Dihydrochloride ((–)-5·2HCl). To a solution of (–)-9 (2.3 g, 0.01 mol) in 25 mL of anhydrous THF was added borane-tetrahydrofuran complex (50 mL, 1 M solution in THF) dropwise under N₂ at room temperature. The resulting mixture was stirred at 50 °C for 1 h and cooled, and then water (5 mL) and concentrated aqueous HCl (10 mL) were added. The THF was evaporated and 25% aqueous NaOH (30 mL) was added to the water phase. The precipitate was collected by filtration, washed with water, and dissolved in hot EtOAc. The solution was dried (MgSO₄) and concentrated. The precipitated base was collected by filtration, washed with EtOAc, and converted into the dihydrochloride salt, which was recrystallized from CH₃OH to afford 1.4 g (50%), mp 296–298 °C; $[\alpha]_D^{20} -67.2^\circ$ (c 1, CH₃OH); ee > 96% (detection limit), determined with Yb(fod)₃ as chiral shift reagent; ¹H NMR (CD₃OD) δ 3.67 (m, 1 H), 3.12 (t, *J* = 9 Hz, 2 H), 1.99–3.24 (m, 6 H), 1.94 (m, 2 H), 1.06 (t, *J* = 8 Hz, 3 H), NH in the solvent blind peak. Anal. (C₁₀H₁₇N₃S·2HCl) C, H, Cl, N.

(+)-2-Amino-6-propyltetrahydrobenzothiazole Dihydrochloride ((+)-5·2HCl) was obtained from (+)-9 in the same

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manner as (2)-5-2HCl in 58% yield, mp 297-298 °C; $[\alpha]_D^{20} +66.0^\circ$ (c 1, CH₃OH); ee > 96% (detection limit), determined with Yb(fod)₃ as chiral shift reagent; ¹H NMR (CD₃OD) δ 3.67 (m, 1 H), 3.12 (t, *J* = 9 Hz, 2 H), 1.99-3.24 (m, 6 H), 1.94 (m, 2 H), 1.06 (t, *J* = 8 Hz, 3 H), NH in the solvent blind peak. Anal. (C₁₀H₁₇N₃S₂HCl) C, H, Cl, N.

Pharmacology. DA Synthesis Rate. According to the method of Walters and Roth,²⁵ male rats (200-250 g) were injected with saline (0.9% NaCl, 1 mL/kg sc) or drugs at various doses. After 5 min GBL (750 mg/kg) and 5 min later the DOPA decarboxylase inhibitor NSD 1015 (100 mg/kg) were injected intraperitoneally. Forty minutes after drug administration, the rats were decapitated, and the corpus striatum was dissected on ice, weighed, and immediately homogenized in a mixture of 2 mL of 0.4 N perchloric acid, 0.05 mL of 5% Na₂S₂O₅, 0.1 mL of 10% Na₂EDTA, and 100 ng of 3,4-dihydroxybenzylamine as an internal standard. After homogenization of the tissue, the further clean-up procedure and the determination of the catechols by means of HPLC with electrochemical detection was performed as previously described.^{10,26}

DA Utilization. For the estimation of the DA content following α -MT (250 mg/kg ip 4 h before killing) and the compounds (various doses sc 4 and 2 h before killing) total rat brain without cerebellum was investigated. It was treated and the DA content

was measured as described above. In both experiments control values were obtained by giving saline (0.9%) instead of the drugs under investigation.

DA Receptor Binding. Dopamine receptor binding was performed as described²⁷ with [³H]spiperone as radioactive ligand in a concentration of 0.5 nM.

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Registry No. (±)-4 (free base), 106006-79-5; (±)-4-2HCl, 106006-72-8; (+)-4 (free base), 106006-73-9; (+)-4 (L-tartrate), 106006-74-0; (+)-4-2HCl, 106006-75-1; (-)-4 (free base), 106006-76-2; (-)-4 (D-tartrate), 106006-77-3; (-)-4-2HCl, 106006-78-4; (R)-5 (free base), 104632-28-2; (R)-5-2HCl, 104632-27-1; (S)-5 (free base), 104632-26-0; (S)-5-2HCl, 104632-25-9; 6, 106160-66-1; 6 (free base), 106092-08-4; (±)-7, 106006-80-8; (±)-8, 106006-83-1; (±)-8-2HBr, 106006-81-9; (±)-8-2HCl, 106006-82-0; (S)-8, 106092-09-5; (S)-8-(L-tartrate) (dihydrate), 106160-67-2; (S)-8-2HCl, 106092-10-8; (R)-8, 106092-11-9; (R)-9, 106006-85-3; (S)-9, 106006-84-2; 4-acetamidocyclohexanone, 27514-08-5; thiourea, 62-56-6; propionic anhydride, 123-62-6.

Supplementary Material Available: Atomic coordinates and geometrical data for compound (-)-8 (9 pages). Ordering information is given on any current masthead page.

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Amnesia-Reversal Activity of a Series of Cyclic Imides[†]

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A series of dihydro-1*H*-pyrrolizine-3,5(2*H*,6*H*)-diones were synthesized and evaluated for their ability to reverse electroconvulsive shock (ECS) induced amnesia in mice. Among the structure-activity relationships explored were the effects of ring size, the presence of heteroatoms (sulfur) in the ring system, and the introduction of alkyl substituents. The optimal ring size for the bicyclic system was 5.5 with dihydro-1*H*-pyrrolizine-3,5(2*H*,6*H*)-dione (3), although some activity was present in the corresponding 5.6 [hexahydro-3,5-indolizinedione (7)] and 6.6 [tetrahydro-2*H*-quinolizine-4,6(3*H*,7*H*)-dione (9)] analogues. Replacement of the C-1 carbon atom in compound 3 with a sulfur [dihydropyrrolo[2,1-*b*]thiazole-3,5(2*H*,6*H*)-dione (10)] abolished activity, and the introduction of methyl groups resulted in poorer biological profiles except when the substitution was made at the 7*a* position [dihydro-7*a*-methyl-1*H*-pyrrolizine-3,5(2*H*,6*H*)-dione (4)]. In several instances, hydrolysis of the parent bicyclic compound was carried out to furnish the corresponding lactam acids, which were further derivatized. Several exhibited interesting activity, especially the 5-oxo-2-pyrrolidinepropanoic acid derivatives such as 5-oxo-2-pyrrolidinepropanoic acid (12), 5-oxo-2-pyrrolidinepropanoic acid phenylmethyl ester (17), 5-oxo-2-pyrrolidinepropanoic acid (3-chlorophenyl)methyl ester (20), *N*-4-pyridyl-5-oxo-2-pyrrolidinepropanoic acid amide (25), and *N*-(2,6-dimethylphenyl)-5-oxo-2-pyrrolidinepropanoic acid amide (27). Compound 3 (CI-911; rolziracetam) was also observed to improve performance on a delayed-response task in aged rhesus monkeys and was selected for evaluation in cognitively impaired human subjects on the basis of its biological profile and a wide margin of safety in animals.

Many substances are known to affect intellectual performance in humans, usually producing an impairment of cognition. Several of these have been used by neurobiologists to study the brain systems responsible for cognitive functions in animals.¹ Unfortunately, no drugs have been identified yet that are useful in the prevention or treatment of the most prominent human cognitive disorders such as mental retardation, learning disabilities, or

the dementias [primary degenerative dementia (PDD); Alzheimer's disease].²

We previously reported on the cognition-activating effects of 3-phenoxy-pyridine (CI-844, compound 1).³ This compound improved performance in a single-trial passive

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